STEREOCONTROLLED SYNTHESIS OF NEW TETRAHYDROFURO[2,3-*d*]THIAZOLE DERIVATIVES VIA ACTIVATED VINYLOGOUS IMINIUM IONS

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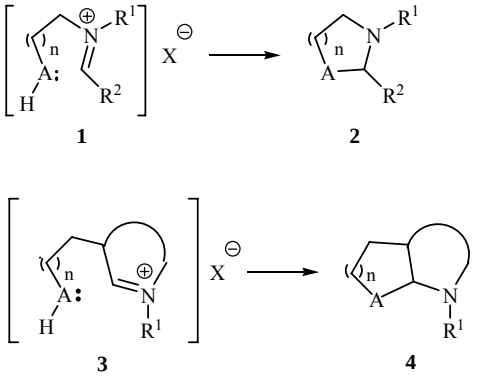
Abstract-Intramolecular heterocyclization of (*Z*)-5-(2-hydroxyethyl)-3-methyl-4-oxothiazolidines, bearing electron-withdrawing groups conjugated to an exocyclic double bond at C(2)-position, afforded under reductive conditions, not easily accessible *cis*-tetrahydrofuro[2,3-*d*]thiazole derivatives. The reactions of these functionalized push-pull β-enamines occur in a stereocontrolled fashion via activated vinylogous *N*-methyliminium ions, which are trapped by an internal hydroxyethyl group.

*Key words***:** Thiazolidines, vinylogous *N*-iminium ion, heterocyclization,

1. Introduction

In recent years, a variety of acyclic and cyclic iminium ions with a nucleophilic tether, exemplified by general structures **1** and **3** (Scheme 1), have been successfully used for heterocyclization reactions giving rise to nitrogen-containing heterocycles **2** and **4**, respectively.[1]



Scheme 1

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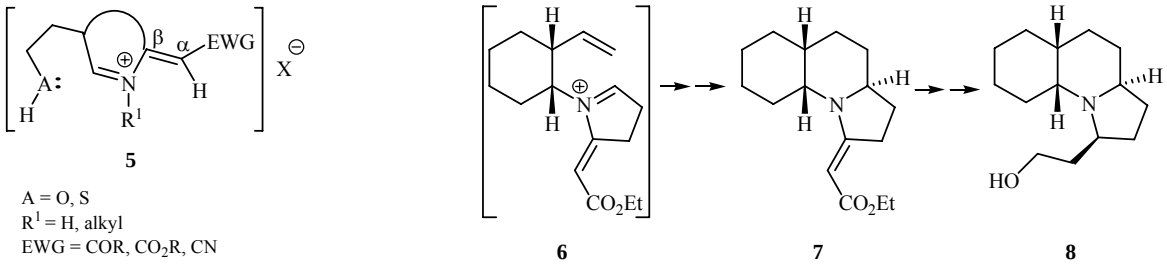
An abundance of strategic preparations of different ring systems with five to eight atoms, based on an *endo*-mode cyclization of iminium ion **1**, bearing properly located oxygen,[2] sulfur[3] or nitrogen[4] as heteroatom, or nonaromatic and aromatic C=C bond as a π-nucleophile,[5] has confirmed a wide scope of this process. Likewise, the literature documents that numerous synthetically and medicinally important condensed heterocycles, can be derived by an *exo*-type cyclization of the key cyclic intermediate **3**.[6] Extensive experimental evidence underlines the correlation between the presence of electron-withdrawing groups (EWG), such as the acyl, tosyl, COOR or $CONR_2$, at the nitrogen atom of iminium ions **1** and **3**, and their increasing cationic character, thus, making them more reactive toward nucleophiles.[1,7] The synthetic utility of vinylogous iminium ions **5** for ring closure reactions has been also examined, however, in an exceedingly limited number of cases[8] (Scheme 2). Within this context, Hart[8a] has reported one of the rare examples when a vinylogous iminium ion **6** undergoes intramolecular π-cyclization, forming a useful tricyclic intermediate **7**, *en route* to envisioned synthesis of the alkaloid depentylperhydrogephyrotoxin **8**.[9]

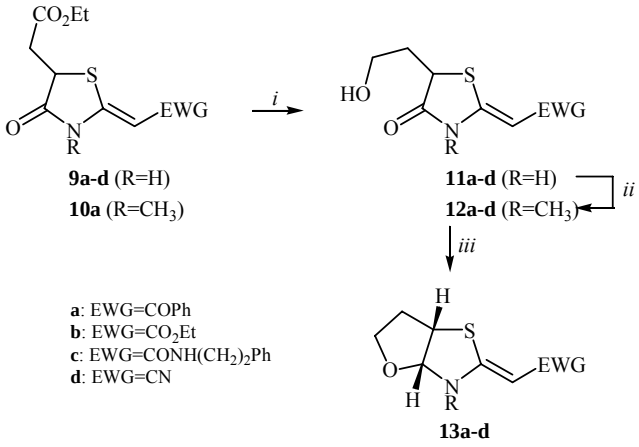


Scheme 2

Now we wish to demonstrate an ability of new vinylogous *N*-alkyliminium ions of type **5**, possessing the hydroxyethyl group as an internal nucleophile (A = O; R^1 = Me), to participate in heterocyclization, that is, as one would anticipate, strongly driven by the presence of various electron-withdrawing groups at the α-position of the C=C bond. Therefore, our studies, described below, represent to the best of our knowledge, (i) the first example of 5-*exo*-trig intramolecular cyclization of push-pull 3-methyl-(*Z*)-4-oxothiazolidine alcohols **12a-d**, obtained from 2-alkylidene-5-carboethoxymethyl-4-oxothiazolidines **9a-d**,[10] to new *cis*-condensed thiazolidine compounds **13a-d** (Scheme 3), including (ii) the determination of the stereochemistry by a single-crystal X-ray analysis of a representative of the series, *cis*-(*Z*)-2-(tetrahydro-3-methylfuro[2,3-*d*]thiazol-2(5*H*)-ylidene)-1-phenylethanone **(13a)**.

2. Results and discussion

In our preliminary study,[11] thiazolidine β-enamino derivatives **9a-d**, containing the carboethoxymethyl substituent at C(5) position, were found to react with $NaBH_4$ in ethanol to afford in chemoselective fashion the corresponding alcohols **11a-d** (R=H). To our surprise *N*-methyl substituted 4-oxothiazolidine derivative **10a** having the (*Z*)-configuration, presently confirmed by a single-crystal X-ray structure (Figure 1), was converted under analogous conditions into the bicyclic product **13a**, albeit in a small yield (21%).



(*i*) $NaBH_4$ (4.5-9 equiv), C_2H_5OH, 2h, reflux (*ii*) K_2CO_3, CH_3I, C_2H_5OH, 1h, room temp.
(*iii*) $NaBH_4$ (2.3 equiv), C_2H_5OH, 4h, room temp.

Scheme 3

Despite the considerable amounts of other products being formed (*vide infra*), this result prompted us to further explore whether the thiazolidines **9a-d** can be employed for the synthesis of not easily obtainable bicyclic products **13a-d**[12] via a *reduction-alkylation-ring closure* sequence, involving the C(5) and C(4) positions of the starting derivatives.[13]

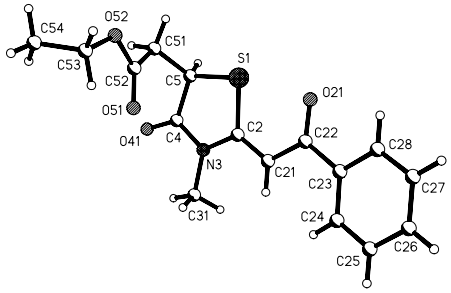
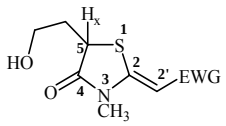


Figure 1. Perspective view of the crystal structure of (*Z*)-(5-ethoxycarbonylmethyl-3-methyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**10a**), showing the crystallographic numbering scheme. Selected bond lengths (Å): S1-C2 1.755(2), S1-C5 1.820(2), C2-N3 1.388(2), C2-C21 1.358(2), N3-C4 1.378(2), C4-O41 1.220(2), C4-C5 1.512(2), C21-C22 1.446(2). The S1···O21 non-bonded distance is 2.605(1) Å.

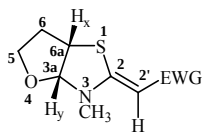
Precursors **9a-d**, required for the synthesis of **11a-d** with built-in alcohol nucleophiles, were obtained by known base-catalyzed reactions of β-oxonitriles and diethyl mercapto-succinate.[10] The unambiguous assignment of the (*Z*)-configuration to the exocyclic C=C bonds of compounds **9a-c** has been established by NOE correlations and crystallographic studies,[10b] whereas the heterocycle **9d**, having the nitrile substituent as EWG, was obtained as a mixture of both isomers. As indicated above, the regioselective reduction of the side-chain acetate group in **9a-d** with excess $NaBH_4$ gave rise to alcohols **11a-d** in good yields (49-64 %), without affecting the enaminone moiety, or affording the products of reductive ring opening. The resistance of this structural fragment to reduction by metal hydrides or catalytic reduction, is considered to reside in strong deactivation of EWG function and C=C bond due to resonance delocalization.[11,14] Standard alkylation of the (*Z*)-**11a-c**, afforded, without configuration change, the corresponding 3-methyl-4-oxothiazolidine alcohols **12a-c** (Table 1, 78-92%) This is expected in view of the greater stability of (*Z*)-configurated thiazolidines **9a-c** in the solid state and in polar solvents, versus the (*E*)-analogs, particularly due to the strong nonbonded electrostatic S---O interaction of the 1,5-intra-type in the former isomers.[15] Interestingly, **12d** (EWG = CN) was also isolated as a single (*Z*)-isomer. Apparently, the steric bias provided by the *N*-methyl substituent is sufficient to fix the (*Z*)-configuration. The ring closure upon treatment of **12a-d** with $NaBH_4$ in ethanol at room temperature, proceeded in a stereocontrolled manner, and the *cis*-fused products **13a-d** were isolated after preparative TLC purification as single *Z*-isomers, in reasonable yields (36-56%, Table 1). Besides the elemental analyses, the spectroscopic results are fully consistent with the structures of the new bicyclic products **13a-d**. The IR spectra of **13a-d**, recorded in the solid state (KBr pellet) show a strong band within the 1080-1030 cm^{-1} range due to the characteristic asymmetric stretching of the C-O bond in the tetrahydrofuran ring. Another diagnostic and strong band at ~ 1580 cm^{-1}, present in all IR spectra of derivatives **13a-d**, is assigned to the exocyclic C=C bond of an enamine moiety.[16] The two five-membered rings are *cis*-fused. The conclusive structural evidence stems from ^{1}H-NMR data: the vicinal coupling constants J_{XZ} being alike (6.2-6.6 Hz) in all bicyclic structures (Table 1, entries 2,4,6 and 8) closely match those of comparable systems reported previously.[12c-e] In addition, the *cis*-geometry was also supported by the *HH* ROESY experiment. Thus, the proton attached to C-6a of **13a** which resonates at δ 4.12, assuming the β-orientation, exhibits NOE interactions with H-3a and H-6 positioned

at the β-face. From the *HH* ROESY spectrum of **13a** the correlation between the N-CH_3 and vinyl proton confirmed the (Z)-configuration of the C=C bond.

Table 1. Yields and selected ^{1}H and ^{13}C NMR chemical shifts (ppm) of 4-oxothiaziolidine alcohols **12a-d** in DMSO-d_6 and bicyclic thiazolidine derivatives **13a-d** in $CDCl_3$



12a-d



13a-d

Entry	Compound/EWG	=CH	H_X	H_Y	J_{XY} (Hz)	C(2)	=CH	$\Delta\delta_{C2,C2'}$	Yield (%)[a]
1	(*Z*)-**12a** /COPh	6.92	4.12[b]			161.4	95.4	66.0	86
2	(*Z*)-**13a** /COPh	6.04	4.12	5.67	6.5	165.7	87.5	78.0	56
3	(*Z*)-**12b** /CO_2Et	5.57	4.12 [b]			158.5	89.4	69.1	92
4	(*Z*)-**13b** /CO_2Et	4.84	4.10	5.61	6.2	162.9	79.6	83.3	36
5	(*Z*)-**12c** /CONH(CH_2)Ph	5.55	3.97 [b]			166.1	93.2	72.9	78
6	(*Z*)-**13c** / CONH(CH_2)Ph	4.67	4.06	5.55	6.2	166.0	82.2	83.8	40
7	(*Z*)-**12d** /CN	5.27	4.41 [b]			160.4	67.1	93.3	80
8	(*Z*)-**13d** /CN	3.94	4.25	5.65	6.6	160.8	55.8	105.0	40

[a] Yields refer to pure isolated products.
[b] Part of an ABX spin-coupling system with protons of the neighboring methylene group.

The selected ^{13}C NMR shift differences between the olefinic carbon atoms, i.e. $\Delta\delta_{C(2)C(2')}$ values in compounds **12** and **13** are worth noting (Table 1). They indicate a charge separation of C=C bond as a measure of the push-pull character[17] within the condensed thiazolidines **13**, relative to 4-oxothiazolidine alcohols **12**. Larger $\Delta\delta_{C(2)C(2')}$ values (78-82 ppm) in the bicyclic derivatives **13a-d** from 78-105 ppm, respectively (Table 1, entries 2,4,6 and 8) versus the corresponding $\Delta\delta_{C(2)C(2')}$ values (66-93 ppm) in alcohols **12a-d** (Table 2, entries 1,3,5 and 7) correlate with an increase of the push-pull effect in **13**.[18] An explanation is in accord with the presence of the more effective electron-donor (i.e. an amine) in the fused thiazolidines **13** in comparison to an amide functionality in substrates **12**.

Further evidence, supporting unequivocally the *cis*-ring juncture stereochemistry and (Z)-configuration assigned to **13a-d**, was provided by an X-ray crystal structure analysis of the representative of the series **13a** (Figure 2).

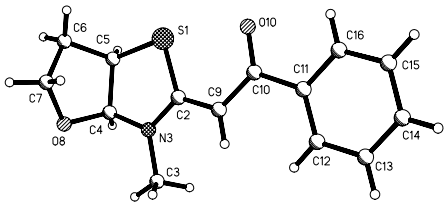


Figure 2. Perspective view of the crystal structure of (*Z*)-2-(tetrahydro-3-methylfuro[2,3-*d*]thiazol-2(5*H*)-ylidene)-1-phenylethanone (**13a**). Selected bond lengths (Å): S1-C2 1.746(1), S1-C5 1.828(1), C2-N3 1.347(2), C2-C9 1.381(2), N3-C4 1.451(2), C4-O8 1.420(2), C4-C5 1.544(2), C9-C10 1.426(2).

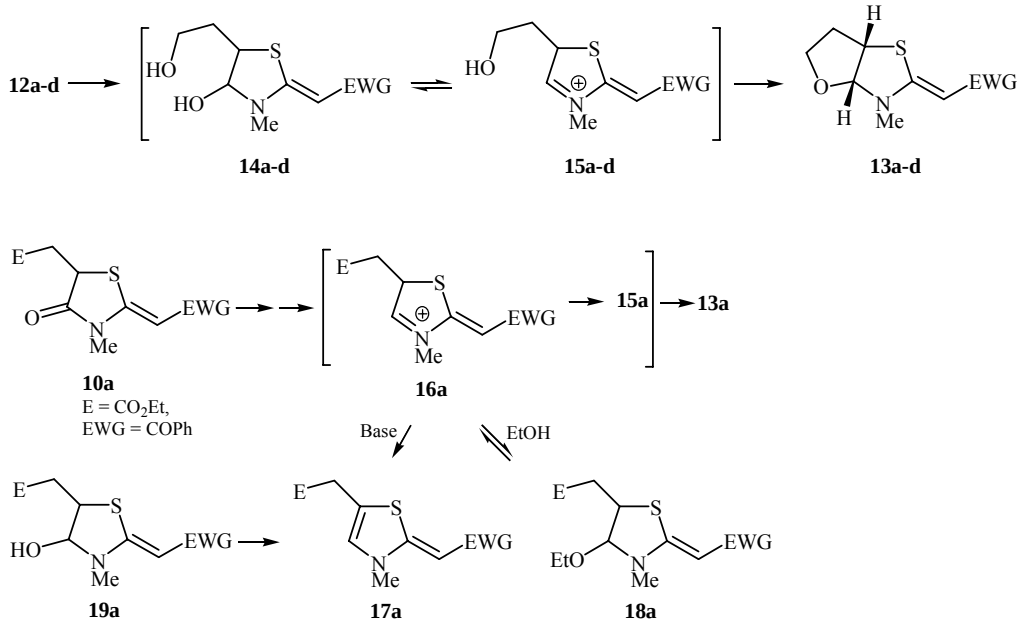
Compound **13a** crystallizes in the space group $P2_1/c$, but with two molecules in the asymmetric unit. Figure 2 shows a perspective view of one molecule with selected bond lengths. The geometries of the two independent molecules are almost identical. The crystal structure confirms the geometry of the fused-ring junction (*cis*) and the exocyclic double bond (*Z*). The thiazolidine ring is almost planar *cis* (mean deviation from the meanplane = 0.013 and 0.18 Å, for the two independent molecules) as a consequence of containing an unsaturated linkage. The conformation of the side chain is similar to that in **10a** (Figure 1), although the non-bonded S-O distance[10b,18] has increased slightly to 2.724(1) and 2.729(1) Å, for the two independent molecules.

In accordance with the spectroscopic results, semiempirical calculations with MOPAC (PM3, geometry optimisation) and ab initio calculations with Gaussian (HF, 6-31G*, geometry optimisation) show that the *cis*-isomers **13a-d** are preferred from an energetic point of view. As exemplified for **13a**, the *cis*-isomer is 19.5 kcal more stable as calculated by MOPAC, or 16.5 kcal according to a Gaussian calculations (Figure 3).

Figure 3. The *cis*- and *trans*-configurations of **13a**

Visual inspection of the three-dimensional models depicted in Fig. 3 clearly indicate that the large energy difference should be attributed to a combination of severe angle strain and nonbonded transannular repulsion imposed upon a *trans*-fusion of the almost flat thiazolidine ring to the tetrahydrofuran ring. As a result, the thiazolidine ring in the *trans*-fused compound **13a** is forced to adopt a relatively nonplanar conformation, where there is no optimal conjugation between nitrogen (and sulfur) and EWG through the intervening C=C bond. Release of the angle strain-constraint in the *cis*-arrangement of the two five-membered rings, in combination with the resonance effect attenuation, is responsible for this exclusive lower energy configuration of the *cis*-isomer **13a**.

On the basis of the experiments presented here, and numerous regioselective hydride reduction of ring substituted cyclic imides to hydroxy lactams,[1c,6a,b,8d,19a] it is clear that the reduction of 4-oxothiazolidine alcohols **12** with $NaBH_4$ in ethanol leads, in a first step, to *in situ* formation of a diol **14** (Scheme 4).



Scheme 4

This initial step sets the stage for the conversion of the diol **14** into the vinylogous *N*-methyliminium ion **15**, having the incorporated hydroxyethyl group at the C(5)-position as a reactive nucleophile. Subsequent intramolecular 5-*exo*-trig heterocyclization by nucleophilic attack onto the iminium π-bond affords the *cis*-fused tetrahydrofurothiazolidine **13**. In general, it has been found that *N*-acyliminium ion cyclization gives rise to a lower yield if the iminium carbon atom is bonded to a carbon-carbon double or triple bond.[20] However, our experimental results indicate that ring closure of vinylogous methyliminium ion **15** is assisted by the electron-withdrawing group at the α-carbon atom of the exocyclic C=C bond. The aforementioned *cis*-disposition of the angular hydrogens in the transition-state structure and in the product **13** involves the minimization of angular strain, thus dictating the stereochemical course of the reaction. The heterocyclization selectivity regarding the **15→13** step has been already established for cyclizations leading to similar bicyclic system.[12c-e] Additional evidence regarding the postulated iminium ion **15** as a key intermediate has been obtained in direct heterocyclization of the *N*-methyl-4-oxothiazolidine **10a** to **13a** (21% yield) under reductive conditions (Scheme 2). The formation of by products, 3-methylthiazole derivative **17a** (18%) and 4-ethoxy-3-methylthizolidine derivative **18a** (1-2%), is consistent with the presence of **16a** as a transient species, thereby also leading to **13a** via **15a**. Another distinct pathway to the double enamine species **17a**, involves dehydration of a hydroxythiazolidine **19a**, obtained by initial hydride reduction of **10a,** thus, reducing the yield of cyclization product **13a**.[20]

In summary, the study on the intramolecular heterocyclization of (*Z*)-5-(2-hydroxyethyl)-3-methyl-4-oxothiazolidines, giving rise to new stereodefined tetrahydrofuro[2,3-*d*]thiazole derivatives, has been presented. The scope and mechanism of this transformation, involving a new type of vinylogous *N*-methyliminium ion, possessing the hydroxyethyl group as the internal nucleophile and different electron-withdrawing groups, at the α-position of the exocyclic C=C bond, were also studied.

3. Experimental

Melting points were determined on a Micro-Heiztisch Boetius PHMK apparatus or Bηchi apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrophotometer and are reported as wave numbers (cm^{-1}). Samples for IR spectral measurements were prepared as KBr disks. The NMR spectra were obtained using a Varian Gemini 2000 instrument (^1H at 200 MHz, ^{13}C at 50.3 MHz). ^{13}C NMR resonance assignments were aided by the use of the DEPT technique to determine numbers of attached hydrogens. ROESY have been performed..... Chemical shifts are reported in parts per million (ppm) on the δ scale from TMS as an internal standard in the solvents specified. Low-resolution mass spectra were recorded using a Finnigan MAT 8230 BE spectrometer at 70 eV (EI). Isobutane was used as the ionizing gas for the chemical ionization (CI) mass spectra. The UV spectra were measured on a Beckman DU-50 spectrophotometer. Analytical thin-layer chromatography (TLC) was carried out on Kieselgel G nach Stahl, and the spots were visualized by iodine. Column chromatography was carried out on SiO_2 (silica gel 60Å, 12-26, ICN Biomedicals). Elemental analyses were performed at the microanalysis laboratory at the Department of Chemistry, University of Belgrade.

3.1. General procedure for the preparation of 3-methyl-4-oxothiazolidine alcohols 12a-d

To a stirred solution of 4-oxothiazolidine alcohol **11** (0.5 mmol) and K_2CO_3 (0.5 mmol) in dry acetone (3-5 mL), protected by aluminum foil, a 10% molar excess of MeI (0.55 mmol) in acetone (~ 1-1.5 mL) was added in one portion at rt. The progress of the reaction was followed by TLC. The reaction mixture was refluxed for an additional 1-2.5 h until consumption of starting material. After evaporation of solvent under reduced pressure, the crude residue was purified by column chromatography (silica gel; toluene/ethyl acetate gradient 100:0 to 50:50, v/v) to afford 3-methyl-4-oxothiazolidine alcohols **12**. Annalytically pure sample was obtained by crystallization from toluene in the case of **12a**, **12b** and **12d** or from chloroform/*n*-hexane mixture for **12c**.

3.1.1. (*Z*)-5-(2-Hydroxyethyl)-3-methyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (12a).

The title compound was obtained as a white solid in 86% yield (90 mg) from 100 mg (0.38 mmol) of **11a** and 60 mg (0.027 mL, 0.42 mmol) of methyl iodide. Mp 134-135 °C; IR (KBr): ν_{max} 3412, 3065, 2922, 2865, 1690, 1626, 1575, 1510, 1464, 1423, 1349, 1225, 1128, 1052, 695, 632 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.75-1.93 (1H, m, $CH_AH_BCH_XS$), 2.16-2.31 (1H, m, $CH_AH_BCH_XS$; the coupling constants of H_A and H_B protons cannot be

determined as signals are of higher order), 3.27 (3H, s, NCH_3), 3.59 (2H, m, CH_2OH), 4.12 (1H, dd, J_{AX}=4.8 Hz, J_{BX}=4.2 Hz, $CH_AH_BCH_XS$), 4.80 (1H, broad t, OH), 6.92 (1H, s, =CH), 7.47-7.63 (3H, m, *p*-Ph and *m*-Ph), 7.83 (2H, dd, $J_{o,m}$=7.8 Hz; $J_{o,p}$=1.8 Hz, *o*-Ph); ^{13}C NMR (DMSO-d_6): δ 30.4 (NCH_3), 35.9 (CH_AH_B), 42.8 (CH_X), 58.5 (CH_2OH), 95.4 (=CH), 127.7 (*m*-Ph), 128.8 (*o*-Ph), 132.4 (*p*-Ph), 138.5 (C_1-Ph), 161.4 (C=), 175.3 (CO_{lactam}), 187.5 (CO_{ketone}); MS (CI): *m/z* 278 (M^+ + 1); UV (DMSO): λ_{max} (ε) 333.9 nm, (33,600). Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05; S, 11.56; Found: C, 60.58; H, 5.48; N, 5.12; S, 11.80.

3.1.2. Ethyl (*Z*)-(5-(2-Hydroxyethyl)-3-methyl-4-oxothiazolidin-2-ylidene)ethanoate (12b).

The title compound was obtained as a white solid in 92% yield (49 mg) from 50 mg (0.22 mmol) of **11b** and 34 mg (0.015 mL, 0.24 mmol) of methyl iodide. Mp 87-89 °C; IR (KBr): ν_{max} 3352, 3065, 2975, 2931, 1711, 1684, 1575, 1472, 1366, 1333, 1279, 1175, 1122, 1044, 862, 791, 768 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.20 (3H, t, *J*=7.2 Hz, CH_2CH_3) 1.69-1.87 (1H, m, $CH_AH_BCH_XS$), 2.13-2.28 (1H, m, $CH_AH_BCH_XS$; the coupling constants of H_A and H_B protons cannot be determined as signals are of higher order), 3.07 (3H, s, NCH_3) 3.55 (2H, m, CH_2OH), 4.09 (2H, q, *J*=7.2 Hz, CH_2CH_3), 4.12 (1H, dd, H_X; J_{AX} and J_{BX} cannot be determined as the signal is buried below the quartet centered at δ 4.09), 4.78 (1H, t, *J*=5.0 Hz, OH), 5.57 (1H, s, =CH), ^{13}C NMR (DMSO-d_6): δ 14.5 (CH_2CH_3), 30.0 (NCH_3), 36.1 (CH_AH_B), 43.3 (CH_X), 58.5 (CH_2OH), 59.4 (CH_2CH_3), 89.4 (=CH), 158.5 (C=), 167.1 (CO_{ester}), 175.2 (CO_{lactam}); MS (CI): *m/z* 245 (M^+ + 1); UV (DMSO): λ_{max} (ε) 282.4 nm, (22,600). Anal. Calcd for $C_{10}H_{15}NO_4S$: C, 48.96; H, 6.16; N, 5.71; S, 13.07; Found: C, 48.95; H, 6.15; N, 5.74; S, 13.35.

3.1.3. (*Z*)-(5-(2-Hydroxyethyl)-3-methyl-4-oxothiazolidin-2-ylidene)-*N*-(2-phenylethyl)ethanamide (12c).

The title compound was obtained as a white solid in 78% yield (40 mg) from 49 mg (0.16 mmol) of **11c** and 25 mg (0.011 mL, 0.18 mmol) of methyl iodide. Mp 145-146 °C; IR (KBr): ν_{max} 3348, ? jos neki signal 3074, 3026, 2923, 2882, 1685, 1640, 1581, 1545, 1475, 1423, 1332, 1298, 1213, 1128, 1128, 1075, 807, 780, 735, 701 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.62-1.79 (1H, m, $CH_AH_BCH_XS$), 2.01-2.25 (1H, m, $CH_AH_BCH_XS$; the coupling constants of H_A and H_B protons cannot be determined as signals are of higher order), 2.72 (2H, *J*=7.2 Hz, CH_2Ph), 3.02 (3H, s, NCH_3) 3.30 (2H, m, CH_2NH), 3.54 (2H, m, CH_2OH), 3.97 (1H, dd, J_{AX}=9.6 Hz, J_{BX}=3.7 Hz, $CH_AH_BCH_XS$), 4.73 (1H, broad t, *J*=5.2 Hz, OH), 5.58 (1H, s, =CH), 7.20-7.33 (5H, m, Ph), ^{13}C NMR (DMSO-d_6): δ 29.6 (NCH_3), 35.4 (CH_AH_B), 36.4 (CH_2Ph), 40.0 (CH_2NH), 42.4 (CH_X), 58.3 (CH_2OH), 93.2 (=CH), 126.0 (*p*-Ph), 128.3 (*o*-Ph), 128.6 (*m*-Ph), 139.5 (C_1-Ph), 151.4 (C=), 166.1 (CO_{amide}), 174.5 (CO_{lactam}); MS (CI): *m/z* 245 (M^+ + 1); UV (DMSO): λ_{max} (ε) 282.4 nm, (22,200). Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74; S, 10.01; Found: C, 59.94; H, 6.20; N, 8.57; S, 10.07.

3.1.4. (*Z*)-(5-(2-Hydroxyethyl)-3-methyl-4-oxothiazolidin-2-ylidene)ethanenitrile (12d)

The title compound was obtained as a white solid in 80% yield (43 mg) from 50 mg (0.27 mmol) of **11d** and 42 mg (0.019 mL, 0.30 mmol) of methyl iodide. Mp 106-107 °C; IR (KBr): ν_{max} 3466, 3076, 2948, 2888, 2203, 1718, 1585, 1424, 1374, 1317, 1121, 914, 723

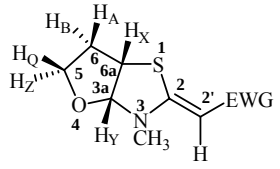
cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.78-1.96 (1H, m, CH_AH$_B$CH$_X$S), 2.17-2.32 (1H, m, CH$_A$$H_BCH_X$S; the coupling constants of H_A and H_B protons cannot be determined as signals are of higher order), 3.04 (3H, s, NCH_3) 3.50-3.60 (2H, m, CH_2OH), 4.41 (1H, dd, J_{AX}=9.8 Hz and J_{BX}=3.8 Hz, CH$_A$H$_B$CH_XS), 4.82 (1H, t, J=5.0 Hz, OH), 5.27 (1H, s, =CH); ^{13}C NMR (DMSO-d_6): δ 29.7 (NCH_3), 35.7 (CH$_A$H$_B$), 45.7 (CH$_X$), 58.5 (CH_2OH), 67.1 (=CH), 118.0 (CN), 160.4 (C=), 174.4 (CO_{lactam}); MS (CI): *m/z* 199 (M^+ + 1); UV (DMSO): λ_{max} (ε) 273.4 nm, (19,000). Anal. Calcd for $C_8H_{10}N_2O_2S$: C, 48.47; H, 5.08; N, 14.13; S, 16.17; Found: C, 48.36; H, 5.06; N, 14.07; S, 16.33.

3.1.5. (*Z*)-(5-Ethoxycarbonylmethyl-3-methyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (10a)

According to general procedure for the preparation of **12a-d** the title compound was obtained as a white solid in 86% yield (90 mg) from 100 mg (0.33 mmol) of **9a** and 51 mg (0.022 mL, 0.36 mmol) of methyl iodide. Mp 114-115 °C; IR (KBr): ν_{max} 3245, 3069, 2986, 2926, 1731, 1706, 1627, 1598, 1575, 1515, 1465, 1419, 1350, 1224, 1196, 1128, 1051, 1000, 791 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.17 (3H, t, J=7.0 Hz, CH_2CH_3), 2.94 (2H, m, C$H_A$$H_BCH_X$S; the coupling constants of H_A and H_B protons cannot be determined as signals are of higher order), 3.28 (3H, s, NCH_3), 4.09 (2H, q, J=7.0 Hz, CH_2CH_3), 4.31 (1H, dd, J_{AX}=7.0 Hz, J_{BX}=4.6 Hz, CH$_A$H$_B$CH_XS), 6.95 (1H, s, =CH), 7.48-7.64 (3H, m, *p*- and *m*-Ph), 8.04 (2H, $J_{o,m}$=8.0 Hz; $J_{o,p}$=1.6 Hz, *o*-Ph); ^{13}C NMR (DMSO-d_6): δ 14.2 (CH_2CH_3), 30.5 (NCH_3), 36.3 (CH$_A$H$_B$), 41.1 (CH$_X$), 60.8 (CH_2CH_3), 95.5 (=CH), 127.8 (*m*-Ph), 128.8 (*o*-Ph), 132.4 (*p*-Ph), 138.3 (C_1-Ph), 161.2 (C=), 170.3 (CO_{ester}), 174.5 (CO_{lactam}), 187.8 (CO_{ketone}); MS (EI): *m/z* (rel. intensity) 319 (M^+, 100), 302(3), 274(13), 245(100), 228(45), 168(63), 131(10), 105(67), 82(64), 77(56), 55(31); UV (DMSO): λ_{max} (ε) 336.0 nm, (25,600). Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.36; N, 4.37; S, 10.04; Found: C, 59.88; H, 5.32; N, 4.39; S, 10.13.

3.2. General procedure for the preparation of (*Z*)-2-(tetrahydro-3-methylfuro[2,3-*d*]thiazol-2-ylidene derivatives 13a-d

To a solution containing 0.1 mmol of *N*-methyl-4-oxothiazolidine alcohol **12** in 5 mL of dry ethanol, 0.23 mmol of $NaBH_4$ in 5 mL of ethanol was added dropwise (~10 min) with vigorous stirring at rt. After the addition was complete, the yellow reaction mixture was stirred for an additional 4 h until complete disappearance of starting material (TLC), whereupon the solution became colorless. The mixture was concentrated under reduced pressure to a small volume (~2 mL). Then, a 5% aqueous solution of ammonium chloride was added, followed by $CHCl_3$ and the stirring was continued for 30 min. The aqueous layer was extracted with $CHCl_3$ and combined organic fractions were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by thin-layer chromatography (toluene/ethyl acetate as eluant; 40:60, v/v). Annalytically pure samples **13a-d** were obtained by crystallization from *n*-hexane (**13b** and **13d**), or *n*-hexane/toluene mixture (**13a** and **13c**).



13a-d

3.2.1. *cis*-(*Z*)-(3-Methyltetrahydrofuro[2,3-d]thiazol-2(3*H*)-ylidene)-1-phenylethanone (13a)

The title compound was obtained as a white solid in 56% yield (14.7 mg) from 29 mg (0.1 mmol) of **9a**. Mp 121-122 °C; IR (KBr): ν_{max} 3053, 2974, 2939, 1602, 1571, 1525, 1433, 1355, 1264, 1213, 1084, 1061, 1028, 973, 801, 727, 691 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.12 (1H, dd broad, J_{AB}=12.6 Hz, J_{AQ}=4.8 Hz, J_{AX}=0.9 Hz, J_{AZ}=1.0 Hz, CH_AH$_B$CH$_X$S), 2.33 (1H, ddt, J_{AB}= 12.9 Hz, J_{BQ}=11.1 Hz, J_{BX}=J_{BZ}=7.4 Hz, CH$_A$$H_BCH_X$S), 3.10 (3H, s, NCH$_3$), 3.83 (1H, ddd, J_{BQ}=11.1 Hz, J_{QZ} =8.8 Hz, J_{AQ} =5.0 Hz, CH_QH$_Z$O), 4.02 (1H, ddd, J_{QZ}=8.8 Hz, J_{BZ}=7.4 Hz, J_{AZ} =1.0 Hz, CH$_Q$$H_Z$O), 4.12 (1H ddd, 1H, J_{BX}=7.4 Hz, J_{XY}=6.6 Hz, J_{AX}=0.9 Hz, OCH$_Y$CH_XS), 5.67 (1H, d, J_{XY}=6.6 Hz, OCH_YCH$_X$S), 6.08 (1H, s, =CH), 7.36-7.47 (3H, m, *m*- and *p*-Ph), 7.90-7.95 (2H, m, *o*-Ph); ^{13}C NMR ($CDCl_3$): δ 33.7 (N*C*H$_3$), 35.2 (CH$_A$H$_B$), 44.6 (CH$_X$), 65.8 (CH$_Q$H$_Z$), 87.5 (=CH), 99.1 (CH$_Y$), 127.2 (*m*-Ph), 128.2 (*o*-Ph), 131.0 (*p*-Ph), 139.7 (C$_1$-Ph), 165.7 (C=), 186.9 (CO$_{ketone}$); MS (EI, 70 eV): *m/z* (rel. intensity): 261 (M^+, 57), 260 (100), 245 (34), 191 (20), 184 (42), 163 (32), 105 (97), 86 (39), 82 (58), 51 (26); UV (DMSO): λ_{max} (ε) 338.0 nm (19,700); Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.78; N, 5.36; S, 12.27; Found: C, 64.24; H, 5.82; N, 5.30; S, 12.59.

3.2.2. *cis*-(*Z*)-Ethyl (3-methyltetrahydrofuro[2,3-d]thiazol-2(3*H*)-ylidene)acetate (13b)

The title compound was obtained as a white solid in 36% yield (20 mg) from 60 mg (0.25 mmol) of **9a**. Mp 48-49 °C; IR (KBr): ν_{max} 3068, 2976, 2948, 2884, 1672, 1567, 1437, 1367, 1243, 1156, 1092, 1046, 1000, 963, 896, 779, 713 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.26 (3H, t, *J*=7.1 Hz, CH$_2$CH_3) 2.11 (1H, dd broad J_{AB}=12.9 Hz, J_{AQ}=4.9 Hz, J_{AX}~0 Hz, J_{AZ}=1.0 Hz, CH_AH$_B$CH$_X$S), 2.29 (1H, ddt, J_{AB}= 12.9 Hz, J_{BQ}=11.0 Hz, J_{BX}=J_{BZ}=7.2 Hz, CH$_A$$H_BCH_X$S), 2.94 (3H, s, NCH$_3$), 3.83 (1H, ddd, J_{BQ}=11.0 Hz, J_{QZ} =8.6 Hz, J_{AQ} =4.9 Hz, CH_QH$_Z$O), 3.98 (1H, ddd, J_{QZ}=8.6 Hz, J_{BZ}=7.2 Hz, J_{AZ} =1.0 Hz, CH$_Q$$H_Z$O), 4.10 (1H dd, 1H, J_{BX}=7.2 Hz, J_{XY}=6.2 Hz, OCH$_Y$CH_XS), 4.15 (2H, q, *J*=7.2 Hz, CH_2CH$_3$), 4.84 (1H, s, =CH), 5.61 (1H, d, J_{XY}=6.2 Hz, OCH_YCH$_X$S); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH$_2$*C*H$_3$), 33.0 (N*C*H$_3$), 35.3 (CH$_A$H$_B$), 44.4 (CH$_X$), 59.1 (*C*H$_2$CH$_3$), 65.6 (CH$_Q$H$_Z$), 79.6 (=CH), 99.5 (CH$_Y$), 162.9 (C=), 169.1 (CO$_{ester}$); MS (CI): 230 (M^++ 1)); UV (DMSO): λ_{max} (ε) 279.0 nm (23,400); Anal. Calcd for $C_{10}H_{14}NO_3S$: C, 52.38; H, 6.59; N, 6.11; S, 13.98; Found: C, 52.24; H, 6.61; N, 6.07; S, 14.00.

3.2.3. *cis*-(*Z*)-(3-Methyltetrahydrofuro[2,3-d]thiazol-2(3*H*)-ylidene)-*N*-phenylacetamide (13c)

The title compound was obtained as a white solid in 40% yield (28 mg) from 75 mg (0.23 mmol) of **12c**. Mp 151-153 °C; IR (KBr): ν_{max} 3303, 3063, 3026, 2925, 2875, 1627, 1561, 1436, 1383, 1254, 1196, 1082, 1028, 989, 778, 750, 703 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.10 (1H, dd broad, J_{AB}=12.6 Hz, J_{AQ}=5.0 Hz, J_{AX}~0 Hz, J_{AZ}=1.2 Hz, CH_AH$_B$CH$_X$S), 2.26 (1H, ddt, J_{AB}= 12.6 Hz, J_{BQ}=10.7 Hz, J_{BX}=J_{BZ}=7.2 Hz, CH$_A$$H_BCH_X$S), 2.83 (2H, t, *J*=7.0 Hz, CH$_2$Ph), 2.88 (3H, s, NCH$_3$), 3.56 (2H, m, *J*=7.0 and 6.2 Hz, CH_2NH), 3.86 (1H, ddd, J_{BQ}=10.8 Hz, J_{QZ} =8.6 Hz, J_{AQ} =5.0 Hz, CH_QH$_Z$O), 3.95 (1H, ddd, J_{QZ}=8.6 Hz, J_{BZ}=7.2 Hz, J_{AZ} =1.2 Hz, CH$_Q$$H_Z$O), 4.06 (1H dd, 1H, J_{BX}=7.2 Hz, J_{XY}=6.2 Hz, OCH$_Y$CH_XS), 4.67 (1H, s, =CH), 5.55 (1H, d, J_{XY}=6.2 Hz, OCH_YCH$_X$S), 7.19-7.30 (5H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 29.6 (N*C*H$_3$), 35.3 (CH$_A$H$_B$), 36.3 (CH$_2$Ph), 40.5 (CH$_2$NH), 44.6 (CH$_X$), 65.6 (OCH$_2$), 82.3 (=CH), 99.1 (CH$_Y$), 126.3 (*p*-Ph), 128.5 (*o*-Ph), 128.9 (*m*-Ph), 139.5 (C$_1$-Ph),

166.0 (C=), 162.1 (CO_{amide}); MS (ESI): Calcd for $C_{16}H_{21}N_2O_2S$: 305.13182 ($M + H^+$); Found: 305.1318; UV (DMSO): λ_{max} (ε) 277.0 nm (12,900).

3.2.4. *cis*-(*Z*)-(3-Methyltetrahydrofuro[2,3-d]thiazol-2(3*H*)-ylidene)acetonitrile (13d)

The title compound was obtained as a white solid in 40% yield (7.5 mg) from 20 mg (0.1 mmol) of **12d**. Mp 59-61 °C; IR (KBr): ν_{max} 3061, 2927, 2860, 2187, 1578, 1423, 1395, 1310, 1259, 1092, 1034, 964, 896, 859, 691 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.12 (1H, dd broad, J_{AB}=13.3 Hz, J_{AQ}=5.1 Hz, J_{AX}=1.0 Hz, J_{AZ}=1.1 Hz, $CH_AH_BCH_XS$), 2.32 (1H, ddt, J_{AB}= 13.3 Hz, J_{BQ}=11.0 Hz, J_{BX}=J_{BZ}=7.4 Hz, $CH_AH_BCH_XS$), 2.88 (3H, s, NCH_3) 3.88 (1H, ddd, J_{BQ}=11.0 Hz, J_{QZ} =8.9 Hz, J_{AQ} =5.1 Hz, CH_QH_ZO), 3.94 (1H, s, =CH), 4.04 (1H, ddd, J_{QZ}=8.9 Hz, J_{BZ}=7.4 Hz, J_{AZ} =1.2 Hz, CH_QH_ZO), 4.25 (1H, ddd, J_{XY}=6.6 Hz, J_{BX}=7.4 Hz, J_{AX}=1 Hz, $CH_AH_BCH_XS$), 4.82 (1H, t, J=5.0 Hz, OH), ^{13}C NMR (DMSO-d_6): δ 29.7 (NCH_3), 35.7 (CH_AH_B), 45.7 (CH_X), 58.5 (CH_2OH), 67.1 (=CH), 118.0 (CN), 160.4 (C=), 174.4 (CO_{lactam}); MS (CI): *m/z* 199 (M^+ + 1); UV (DMSO): λ_{max} (ε) 264.0 nm, (26,100). Anal. Calcd for $C_8H_{10}N_2OS$: C, 52.7; H, 5.53; N, 15.37; S, 17.59; Found: C, 52.77; H, 5.59; N, 15.06; S, 17.56.

3.3. Crystal structure determination of compounds 10a and 13a

Data were collected with a Siemens SMART CCD area detector, using graphite monochromatized MoKα radiation (λ = 0.71073 Å). The structures were solved by direct methods using SHELXS[21] and refined on F^2, using all data, by full-matrix least-squares procedures using SHELXTL.[22] Hydrogen atoms were included in calculated positions, with isotropic displacement parameters 1.2 times the isotropic equivalent of the carrier carbons.
Full tables of atom coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre. CCDC 265572 and 265573 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) + 44-1223/336-033; Email: deposit@ccdc.cam.ac.uk].

Crystal data for 10a: $C_{16}H_{17}NO_4S$, MW 319.37, monoclinic, $P2_1/c$, a = 12.2698(16), b = 12.5920(16), c = 10.1610(13) Å, β = 100.097(2) °, V = 1545.6(3) $Å^3$, Z = 4, T = -183 °C, F(000) = 672, μ (MoKα) = 0.227 mm^{-1}, D_{calcd} = 1.372 $g.cm^{-3}$, $2\theta_{max}$ 53 ° (CCD area detector, 99.2 % completeness), $wR(F^2)$ = 0.0756 (all 3151 data), R = 0.0327 (2135 data with $I > 2\sigma I$).

Crystal data for 13a: $C_{14}H_{15}NO_2S$, MW 261.33, monoclinic, $P2_1/c$, a = 21.7289(13), b = 7.7567(4), c = 15.5614(9) Å, β = 110.413(1) °, V = 2458.1(2) $Å^3$, Z = 8, T = -183 °C, F(000) = 1104, μ (MoKα) = 0.256 mm^{-1}, D_{calcd} = 1.412 $g.cm^{-3}$, $2\theta_{max}$ 53 ° (CCD area detector, 99.5 % completeness), $wR(F^2)$ = 0.0828 (all 5018 data), R = 0.0311 (4543 data with $I > 2\sigma I$).

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